REMARKS

The Examiner has restricted the claims to Group I to a plant and Group II to a method of using a plant. Applicant elects Group II to the method of using a plant, claims 33-39, 42 and 43. Claims 44-48 are added with this amendment.

Applicant traverses the finality of the office action, in that this is the first time the Examiner has rejected the claims under section 103, and the first opportunity the Applicant has for responding to same. The Applicant respectfully submits it was not the amendment of the claims, but pointing out that the Koprowski reference did not show the invention within the four corners that resulted in withdrawal of the novelty rejection and presentation for the first time of the obviousness rejection. In the interest of expediting prosecution, the Applicant has presented this amendment with an RCE continuation.

The Applicant also appreciates the Examiner's withdrawal of prior rejections. The claims are currently rejected under section 103 as obvious over Goodman in view of Koprowski et al. The Examiner finds Goodman teaches the expression of heterologous proteins in plants, but does not teach a fish antigen. Koprowski is cited for teaching a plant and seed infected with a genetically modified microorganism expressing a fish antigen. the Examiner indicates it would be obvious to express the fish antigen of Koprowski using the plant expression system of Goodman. Further, the Examiner believes Goodman inherently would express the antigen at 0.1% total soluble protein and induce an immunogenic response.

The rejection is respectfully traversed on several grounds. First, expressing in a plant an antigen to a pathogen cannot predictably result in a protein produced by the plant machinery that will be in proper form and folded such that when orally administered to the fish, will result in a protective response. Although the Examiner cites Goodman, that reference was entirely related to expressing proteins in plants that would be orally administered to mammals to produce an immune response, not fish. The Examiner is referred to the accompanying declaration of Dr. Linda Bootland, one of the inventors and an expert on fish biology. Fish are cold blooded, and their digestive system and immune and protective response are different from mammals. As she notes, it has been possible in the past to obtain an antibody response when fish are administered an antigen, but yet not obtain a protective response, and the animal succumb to the pathogen despite

producing antibodies. See Frost et al., "analysis of the antibody response in Atlantic salmon against recombinant VP2 of infectious pancreatic necrosis virus (IPNV) *Fish and Shellfish Immunology* (1988) 8:447-456 (see page 453, copy accompanying amendment). Other problems which have been acknowledged in producing a protein that will induce an immune response are that the fish digestive system may destroy the protein, and whether the plant can produce a protein that elicits a protective response. See Barratt et al. WO 92/06599, as well as Companjen et al., "Development of a cost-effective oral vaccination method against viral disease in Fish" Midtlyng PF (ed) *Progress in Fish Vaccinology. Dev Biol Basel*, Karger, 2005 vol. 121, pp 143-150. In Barratt the applicant there attempted to avoid the problems by using a water-in-oil emulsion of the antigen, noting, "Particular problems recognized in the oral route are: possible loss of or damage to essential vaccine components during manufacture of the composition; possible loss of water-soluble vaccine components in the aqueous environment in which the fish live; and possible degradation of the vaccine within the intestine of the fish before the vaccine has induced a protective response." (See page 2, line 23 through page 3, line 2). Companjen used anal intubation of fish with a potato-produced protein of heat labile enterotoxin and influenza/parvo fusions, also noting oral vaccination issues include potential for destruction in the intestinal tract, among others. (See page 143-44). The authors noted in their 2005 article that there was uptake in the gut through their non-oral route of transmission, adding, "whether fish are indeed protected upon oral vaccination by plant-produced vaccines has to be determined.

Here, however, the Applicants have demonstrated that protection of fish by plant-produced antigens is possible. The declaration of Dr. Bootland describes experiments in which she orally administered the antigens as produced by the Example 3 of the specification to fish. VP2 and VP3 antigens were produced in plants, and the plant tissue fed to fish. The examiner's attention is directed in particular to Tables 2 and 3 which summarize results when fish were fed either the killed virus, plant tissue without any recombinant protein, and when fed 10%, 20% or 30% meal expressing the VP2 and VP3 linked to (NVA) or without (NVB) a signal sequence. As the graphs demonstrate, mortality rates dropped from over 50% to about 30% (Table 2). Applicants thus have

demonstrated that one skilled in the art can, for the first time, produce in plants a fish antigen that when orally administered to a fish provides protection from a pathogen.

The claims recite a method of using a plant which expresses an amino acid, when orally administered to a fish, results in a protective response in the fish. Goodman, directed solely to producing mammalian proteins, cannot teach the present invention. Indeed, Koprowski 5,935,750 notes "However, only genetically altered microbial mammalian pathogens have been shown to induce an immune response or effective immune protection against a mucosal pathogen." See column 1, lines 34-37. Koprowski then teaches away from the present invention, by instead using microorganisms to infect plants, and using plants as the carrier vehicle, as being better characterized in their system for synthesis of a bioactive compounded. (Col. 1, lines 38-42).

Further, Applicant's claim 42 is directed to a method of using a plant expressing the antigen at levels of at least about at least about 0.1% total soluble protein. Applicant traverses the position that Goodman inherently would produce expression of the fish antigenic protein at these levels. Goodman is directed to expressing mammalian proteins, not fish antigen proteins in plants, and therefore is inapplicable. What is more, whether one could achieve levels of expression as recited cannot be inferred from Goodman.

New claims 44 through 48 recited that the plant comprises a sequence encoding an antigen of an organism that causes disease or pathology and when fed or orally administered to a fish, results in protective response in the fish (claims 44, 48); is an infectious pancreatic necrosis virus (claim 45); is VP2 or VP3 (claim 46) or both (claim 47). These claims are yet further attenuated from the teachings of Goodman, as discussed above. Support for the claims is found throughout the specification, including examples 3 and 4.

In light of the foregoing, reconsideration and allowance of the claims is respectfully requested. In the event that any issues remain regarding allowance of the claims an interview with the Examiner is formally requested.

Respectfully submitted,

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